

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

SODIUM HYDROXYMETHYLGLYCINATE

Chemical Code # 5720, Tolerance # 52813

3/17/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No study on file ¹
Chronic toxicity, dog:	No study on file ¹
Oncogenicity, rat:	No study on file ¹
Oncogenicity, mouse:	No study on file ¹
Reproduction, rat:	No study on file ¹
Teratology, rat:	No data gap; no adverse effects indicated
Teratology, rabbit:	No study on file ¹
Gene mutation:	No data gap; no adverse effects indicated
Chromosome effects:	No data gap; no adverse effects indicated
DNA damage:	No data gap; no adverse effects indicated
Neurotoxicity:	No study on file ¹

Toxicology one-liners are attached.

All record numbers through 172170 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T181465

Vidair, 3/17/00

¹ New active ingredient, Sodium Hydroxymethylglycinate, submitted as an antimicrobial for terrestrial non-food use. These studies are not required at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study submitted.

CHRONIC TOXICITY, RAT

No study submitted.

CHRONIC TOXICITY, DOG

No study submitted

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted

REPRODUCTION, RAT

No study submitted

TERATOLOGY, RAT

****52813-005; 172166; “Suttocide A-Oral Developmental Toxicity Study in Rats”** (Margitich, D., Pharmakon Research International, Inc., Waverly, PA, Project ID No. PH 328-SU-002-90, 12/17/90). Twenty seven mated female Sprague Dawley rats were administered test article Suttocide A (50% solution) (Lot No. PLI-4D, assay = 54-57% a.i.) daily during gestation days 6-15 by oral gavage at 0 (water), 150, 300 and 450 mg/kg (a.i.). At necropsy and Cesarean section on day 20, maternal and fetal parameters of development were recorded. Clinical signs included post-dosing salivation at incidence of 0/6/17/27 and “decreased activity” at 0/1/1/11, corresponding to 0/150/300/450 mg/kg. There were no significant effects on dam bodyweights. Food consumption by high dose dams was significantly lower ($p < 0.05$) than that by controls for intervals 6-9 and 9-12 days of gestation (intervals 0-6, 12-15, and 15-20 were not affected). Parameters measured at Cesarean section (rats pregnant, aborted, dams with resorptions, dams with viable fetuses, viable fetuses/dam, post- and pre-implantation loss, fetal sex distribution and fetal weights) were all unaffected by the test article, as were the incidence of fetal malformations and variations. **No adverse effects indicated. Maternal NOEL < 150 mg/kg/day** (based on post-dosing salivation in dams administered 150 mg/kg/day). **Developmental NOEL = 450 mg/kg/day** (based on the absence of effects to the fetuses of dams administered 450 mg/kg/day). **Study acceptable** (Vidair 3/14/00).

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

52813-006; 172167; “Suttocide A-*Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)” (Haworth, S., Microbiological Associates, Bethesda, MD, Project ID No. T2114.501, 9/15/83). *S. typhimurium* tester strains TA98, TA1537 and TA1538 (reverted to histidine autotrophy by frameshift mutation), and tester strains TA100 and TA1535 (reverted by base substitution) were exposed to test article Suttocide A (Lot No. SA-101, 50.5% a.i.) at 0 (water only), 7.5, 50, 250, 375 and 500 ug a.i./plate, with or without activation by an S9 microsomal fraction. Exposure was for 48 hrs at 37°C. Each concentration was plated in triplicate for colony formation. Positive controls were functional. Some bacterial toxicity was noted at the two highest concentrations of test article, since the background bacterial lawn began to thin at these concentrations. The test article did not increase the reversion frequency of each tester strain to twice that of the paired control. Therefore, the test article was not considered mutagenic in this assay. **No adverse effects indicated. Study acceptable (Vidair 3/15/00).

CHROMOSOME EFFECTS

52813-006; 172168; “Micronucleus Test (MNT) on Suttocide A” (SanSebastian, J., Pharmakon Research International, Inc., Waverly, PA, Project ID No. PH 309-SU-001-87, 5/18/87). Fifteen CD-1 mice per sex/dose level were administered test article Suttocide A (Lot No. SA-105, 50% a.i.) by single-dose oral gavage at 0 (water), 375, 625 and 875 mg a.i./kg. A group of 5 males and 5 females received the positive control substance, 60 mg/kg of cyclophosphamide. At 30, 48 and 72 hrs after dosing (30 hr only for the cyclophosphamide group), 5 males and 5 females were sacrificed, their femora removed, and their bone marrow isolated for preparation of slides. One thousand polychromatic erythrocytes (PCE) were scored per animal for micronuclei. A total of 1000 PCEs and NCEs (normochromatic erythrocytes) were also scored per animal to determine the PCE/NCE ratio. Clinical signs exhibited by the high dose animals included decreased activity, piloerection and decreased muscle tone. No animals died. No significant increases in the numbers of micronucleated PCEs were seen at any dose level, relative to controls. Also, the PCE/NCE ratios were unaltered by the test article. In contrast, animals administered cyclophosphamide had significantly increased numbers of micronucleated PCEs ($p < 0.01$) and a significantly decreased PCE/NCE ratio ($p < 0.05$). The data indicate that the test article is not a clastogen. **No adverse effects indicated. Study acceptable (Vidair 3/15/00).

DNA DAMAGE

**52813-006; 172169; “Revised Rat Hepatocyte Primary Culture/DNA Repair Test on Suttocide A” (Stankowski, L., Pharmakon Research International, Inc., Waverly, PA, Project ID No. PH 311-SU-002-90, 1/19/95). Freshly isolated hepatocytes from a Fischer 344 male rat were incubated 18-20 hrs at 37°C with 10 uCi/ml of ³H-thymidine and the following concentrations of test article Suttocide A (Lot No. PL1-4D, 50% a.i.): 0 (water), 2.5, 7.5, 10, 20 and 40 ug a.i./ml. Positive controls were exposed to 0.1 uM 2-acetamidofluorene. Following fixation, autoradiography and staining, three replicate coverslips per test article concentration were used to score a total of 150 cells for net nuclear grain (NNG) counts (nuclear grain counts from which adjacent cytoplasmic grain counts were subtracted). A cell with an NNG of ≥ 5 was considered to be undergoing DNA repair, and a mean NNG value of ≥ 5 for the triplicate samples was considered to be a positive response. Considerable toxicity occurred at the high dose, and only one of three replicate coverslips could be scored. No concentration of test article caused an increase in mean

NNG to ≥ 5 , while the positive control was 9.5. The high dose of Suttocide A did induce a repair response in 29.3% of the cells compared to 0% in the negative control and 95% in the positive control. However, the large degree of cytotoxicity observed at 40 ug/ml, coupled with the lack of a dose-response, suggest that extensive cellular damage may have caused the increase in ^3H -thymidine incorporation, rather than damage specifically to chromosomal DNA. **No adverse effects indicated. Study acceptable** (Vidair 3/16/00).

52813-006; 172170; “In Vivo-In Vitro Rat Hepatocyte Unscheduled DNA Synthesis Assay” (San, R. and Raabe, H., Microbiological Associates, Inc., Bethesda and Rockville, MD, Project ID No. TD994.381, 4/28/94). Male Fischer 344 rats were administered test article Suttocide A (Lot No. SA-152, purity = 50%) by oral gavage at 0 (water, 10 rats), 200 (10 rats), 700 (10 rats) and 2000 (13 rats) mg/kg. After 2-4 and 12-18 hours, at least 3 animals per dose level were sacrificed and hepatocytes isolated from their livers. Positive controls were 200 mg/kg methyl methanesulfonate (2-4 hr sacrifice) and 100 mg/kg 2-acetylaminofluorene (12-18 hr sacrifice). Mortality was 7/13 animals in the high dose group only. At 1.5 to 2.5 hrs after seeding onto coverslips, hepatocytes were incubated in medium containing 10 uCi/ml ^3H -thymidine for 4 hrs. After an additional 17 to 20 hrs incubation in the absence of label, coverslips were processed for autoradiography. At least 50 cells per coverslip and 3 coverslips per animal were scored for net nuclear grain counts (nuclear grain counts from which were subtracted adjacent cytoplasmic grain counts). A positive response was considered to be a net nuclear grain count of at least 5 above the vehicle control. No such positive response was induced by any concentration of test article at either time point. In contrast, positive controls were functional. Therefore, the test article was considered negative for induction of unscheduled DNA synthesis in this assay. **No adverse effects indicated. Study acceptable (Vidair 3/17/00).

NEUROTOXICITY

No study submitted.

SUBCHRONIC STUDIES

52813-003; 172164; “Suttocide A-90-Day (Gavage) Toxicity Study in Rats” (Johnson, W., Food and Drug Research Laboratories, Inc., Waverly, NY, Project ID No. 7824, 5/15/84). Ten Sprague-Dawley rats/sex/dose level were administered test article Suttocide A (Lot No. K24-37A, purity not indicated) daily by oral gavage for 90 consecutive days at 0 (water only), 10, 40 and 160 mg/kg (a.i.). There were no treatment-related mortalities, clinical signs, or effects on bodyweights or food consumption. Hematology, clinical chemistry, urinalysis (performed after 6 and 13 weeks) and ophthalmology (performed at study's end) all failed to identify any consistent toxicological effects produced by the test article. Both absolute and relative organ weights were also unaffected. Gross examination at necropsy identified an increase in abnormalities in females at the two highest dose levels; however, these findings were largely red spots and blanched areas on various organs and thought to be caused by variations in the blood retained at the time of sacrifice, and therefore of no toxicological significance. Microscopic findings were limited to 3/10 males with inflamed lymph nodes of the myocardium in the highest dose group only (females were normal) compared to 0/10 in control males; however, the toxicological significance of these observations is doubtful (see Discussion). **No adverse effects indicated. NOEL (M/F) = 160 mg/kg (based on the absence of toxicity at this, the highest dose tested). **Study acceptable** (Vidair 3/13/00).

52813-004; 172165; “Suttocide A-Repeated Dose Oral Toxicity Study in Rats-28 Day” (Margitich, D., Pharmakon Research International, Inc., Waverly, PA, Project ID No. PH 436-SU-001-90, 12/11/90). Ten Sprague Dawley rats/sex/dose level were administered test article Suttocide A (Lot No. PLI-4D, Purity = 54.4%) daily by oral gavage for 28 consecutive days at 0 (water only), 40, 160 and 640 mg/kg (a.i.). One female in the high dose group died on day 8. This animal had severe gastritis and focal ulceration of the glandular portion of the stomach, which may have contributed to its death. Clinical signs were limited to episodes of salivation at the two highest dose levels. Bodyweights were significantly lower in high dose males relative to controls on day 14 ($p<0.05$) and day 21 ($p<0.01$), but not on day 27. Females were unaffected, as was food consumption in both sexes. On day 28, males exhibited a dose responsive decrease in blood total protein ($p<0.05$) and decreased albumin at the highest dose only ($p<0.01$), both relative to controls. High dose females had lower mean creatinine ($p<0.05$) and total protein ($p<0.05$) and higher mean total bilirubin ($p<0.05$), phosphorous ($p<0.05$) and platelets ($p<0.05$) relative to controls. For high dose females, the mean liver weight normalized to bodyweight was 113% of the control value ($p<0.05$), while male livers were not significantly affected. Gross pathology revealed enlarged adrenals in females (incidence of 0/0/2/4 corresponding to 0/40/160/640 mg/kg) and abnormal glandular mucosa in the stomachs of high dose females (0/0/0/2). Microscopic pathology identified gastritis, with an incidence of 0/0/0/2 for males and 0/0/0/5 for females, corresponding to 0/40/160/640 mg/kg. Females also suffered ulceration of the stomach with an incidence of 0/0/0/3. Ophthalmology prior to sacrifice was normal in all animals. **No adverse effects indicated. NOEL (M/F) = 160 mg/kg (based on lower bodyweights in males, an increased incidence of gastritis in both males and females, and an increased incidence of focal stomach ulceration in females, all fed 640 mg/kg). **Study supplemental** (Vidair 3/13/00).